REMARKS

Claims 71-86 are currently under examination in the Application. By the present amendment, claim 87 is added to specifically recite one embodiment of the present invention. Support for this claim is provided throughout the instant application and claims as filed, including claims 71 and 73, and it does not constitute new matter. The following remarks are provided in response to the Office Action mailed July 20, 2006.

Rejections Under 35 U.S.C.§ 103

Claims 71-86 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over one or more references, including (1) Webb (U.S. Patent No. 5,741,516); Webb in combination with Mehlhorn (U.S. Patent No. 5,762,957); (3) Mehlhorn in view of Webb, and (4) Webb by itself or in combination with Mehlhorn or *vice versa*, further in view of Lenk (U.S. Patent No. 5,262,168). Applicants traverse these bases of rejection and submit that the Examiner has failed to establish a *prima facie* case of obviousness over any of the cited references, alone or in any combination.

As an initial matter, applicants submit that to establish a *prima facie* case of obviousness, it must be shown that the following three requirements are met: (1) the prior art must teach or suggest all of the claim limitations; (2) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; and (3) there must be a reasonable expectation of success. M.P.E.P., 8th Ed. § 2143.

Regarding the second requirement, it is well established that the Examiner must provide objective evidence demonstrating that the prior art taught or suggested the combination or modification leading to the claimed invention. The question cannot "be resolved on subjective belief and unknown authority," *In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002); "it must be based on objective evidence of record." *Id.* at 1343. Accordingly, as summarized in the MPEP (706.02(j)), the initial burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly

suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985) (emphasis added). When the rationale to modify the teachings of a reference to produce a claimed invention is not expressly stated in the prior art, the Examiner must present a convincing line of reasoning supporting the rejection. *Id.*

With respect to the teachings of the references, it is important to remember that a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Furthermore, the correct standard for establishing obviousness is not merely a showing that it would have been "obvious to try" various unspecified combinations of elements. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Instead, the examiner must point to evidence demonstrating that the prior art taught or suggested the combination specifically claimed.

Applicants submit that the cited references, alone or in any combination, fail to teach each element of the claimed invention and further fail to provide any motivation to combine or modify the teachings of the references to achieve the claimed invention. The arguments that the Examiner has set forth are directed to the general concept of kits for producing a liposomal formulation described in Webb, which comprises a vinca alkaloid encapsulated in a liposome composed of sphingomyelin and cholesterol. They do not address the presently claimed kits, which advantageously comprise three distinct components: (i) a first vial comprising a vinca alkaloid solution; (ii) a second vial comprising liposomes comprising sphingomyelin and cholesterol and having an acidic interior and exterior; and (iii) a third vial comprising a buffer solution having a pH higher than the pH of the solution in the second vial, such that combining the solutions of the second and third vials results in the pH of the exterior of said liposomes being neutral. The Examiner has not set forth a reasonable basis from which to conclude that these presently claimed kits are obvious over the cited references, and, thus, has not established a *prima facie* case of obviousness.

Applicants reassert the remarks provided in the Amendment filed May 23, 2006 and submit that these remarks establish the non-obviousness of the presently claimed kits. Additional specific remarks directed to each basis of rejection are provided below in response to the Examiner's arguments set forth in the Office Action mailed July 20, 2006.

1. ***Webb alone***

Claims 71-79 and 81-85 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Webb (5,741,516). Specifically, the Examiner states that Webb discloses a method of preparing liposome-encapsulated vinca alkaloids that includes: (1) preparing vinca alkaloid solution; (2) preparing sphingomyelin/cholesterol liposomes with an acidic interior; and (3) adding disodium hydrogen phosphate to the external medium to create a pH gradient with an external pH of 7.2 to 7.6, which leads to the vinca alkaloid being loaded into the liposome. The Examiner concedes that Webb fails to teach the supply of the reagents used to practice this method in the form of a kit. However, the Examiner asserts that supply of the reagents to prepare vincristine sulfate-loaded liposomes just before use by the method taught by Webb would have been obvious to one of ordinary skill ion the art with a reasonable expectation of success.

Applicants traverse this basis of rejection. The Examiner has failed to establish a *prima facie* case of obviousness, since, *inter alia*, he has provided no evidence that the prior art taught each element of the presently claimed kit or taught or suggested modifying the teachings of Webb to produce the presently claimed kit for use in the treatment of a neoplasia, comprising: (i) a first vial comprising a vinca alkaloid solution; (ii) a second vial comprising liposomes comprising sphingomyelin and cholesterol and having an acidic interior and exterior; and (iii) a third vial comprising a buffer solution having a pH higher than the pH of the solution in the second vial, such that combining the solutions of the second and third vials results in the pH of the exterior of said liposomes being neutral.

In addition to failing to establish a *prima facie* case of obviousness, Applicants also submit that the presently claimed kits possess surprising and unexpected advantages that further demonstrate their nonobviousness.

a. The presently claimed 3-component kits provide surprising and unexpected advantages over the prior art

Applicants submit that the presently claimed 3-component kits offer surprising and unexpected advantages, including enhanced vincristine stability, which would not be evident in light of the teachings of the cited references and are contrary to the understanding in the art at the time the instant application was filed. As described in the previous Declaration submitted by Dr. Thomas D. Madden and further emphasized in the accompanying Declaration of Dr. Thomas D. Madden, the presently claimed kits provide enhanced vincristine stability and a substantially increased shelf-life over the compositions described by Webb (2 years versus 6 months).

Prior to the filing of the instant application, it was understood in the art that vincristine had optimal stability at pH 3.5 to 5.5 (Vendrig *et al.*). Accordingly, the skilled artisan would have believed vincristine sulfate to be stable in the acidic environment of the liposome interior. Surprisingly, however, the present applicants found that vincristine sulfate was unstable when loaded in sphingosomes (see Table 1 of accompanying Declaration of Dr. Thomas D. Madden). It is only this discovery that leads to the presently claimed three component kits, which include the important feature that the vincristine is provided in a separate vial from the acidic liposomes or the alkaline buffer. This feature is directly responsible for the enhanced vincristine stability associated with the presently claimed kits.

Thus, Applicants submit that the presently claimed kits provide surprising and unexpected advantages over the teachings related to liposomal formulations and kits provided by Webb. Applicants also submit that this evidence of nonobviousness also applies to the other bases of rejection under Section 103. Applicants further note that claims 74 and 77-86, as well as new claim 87, are specifically drawn to kits comprising a separate vial comprising vincristine sulfate.

b. Webb fails to provide motivation to achieve the presently claimed 3 component kits

Applicants submit that the Examiner has absolutely failed to provide evidence that the skilled artisan would have been motivated to modify the teachings of Webb to produce

the claimed kit. Indeed, the Examiner has enunciated no basis and has provided no line of reasoning supporting his position that it would have been obvious to the skilled artisan, in light of Webb, to produce a kit containing reagents to prepare vincristine sulfate loaded liposomes just before use by the method taught by Webb. Nowhere does Webb suggest that vinca alkaloid-loaded liposomes should be prepared immediately before use.

The Examiner insists that "supply of the components in a kit form in a highly developed field of liposomes is within the skill of the art, especially when Webb teaches on col. 5, lines 30-35 that sphingosomes containing sphingomyelin and cholesterol are stable to acid hydrolysis" (Office Action mailed July 20, 2006, page 4, lines 18-20). Even assuming *arguendo* that providing liposome-encapsulated vinca alkaloids in kit form was within the skill of the art, this rationale leads only to the concept of a kit generally, and certainly provides no motivation to produce the specifically claimed kits, which comprise three vials containing specifically defined components.

Furthermore, it appears that the Examiner is overlooking the requirement that the prior art reference be considered in its entirety, including those portions that would lead away from the claimed invention. As Applicants pointed out in the Amendment submitted on May 23, 2006, Webb teaches that the drug-loaded liposomes have increased drug retention and stability, and may be packaged or lyophilized and reconstituted with a sterile aqueous solution prior to administration. This is contrary to the idea of preparing drug-loaded liposomes from a kit immediately prior to use and therefore, provides no motivation for the skilled artisan to produce the presently claimed kit. Webb provides absolutely no suggestion to provide the drug separately from the liposomes, and the skilled artisan would clearly not be motivated to do so, given that Webb teaches that drug-loaded liposomes may be prepared in advance and stored prior to use. Clearly, it is simpler for users to merely reconstitute or use pre-loaded liposomes than to load the liposome themselves, with the associated risks of error and inconsistency. Accordingly, if the teachings of Webb are considered as a whole, this reference provides no motivation to produce the presently claimed kits, wherein the drug and the liposomes are provided in separate vials.

c. Knowledge in the prior art teaches away from producing the presently claimed 3-component kits

Applicants submit that general knowledge in the prior art teaches away from producing the presently claimed 3-component kit. In the case of pharmaceutical products such as vinca alkaloid formulations, drug-loaded liposomes suitable for direct administration after constitution of a lyophilized powder are greatly preferred over a kit requiring that the drug is loaded into the liposomes prior to patient administration, for reasons related to both convenience, safety, and efficacy. For example, as described in the accompanying Declaration of Dr. Thomas D. Madden, loading of vinca alkaloids, *e.g.*, vincristine, into liposomes is a time-consuming and exacting procedure, since loading of vincristine into spingomyelin and cholesterol-based liposomes must be performed at 63-65°C for 10 minutes to ensure that all drug is loaded. If loading is not performed correctly, the resulting composition would most likely be less efficacious and potentially have undesirable side-effects. Clearly, an end-user would prefer to avoid the additional time and expense associated with performing loading immediately prior to use by using a preloaded liposomal drug formulation.

In response to Applicants previous arguments on this point, the Examiner stated, "there is nothing in Webb to suggest that the solutions themselves should not be supplied in a kit form." Clearly, a lack of teaching away cannot possibly be considered legally sufficient motivation to modify the teachings of a reference in a particular manner. Even viewed in light most favorable to the Examiner's position, this could only amount to an "invitation to try," which is also a legally insufficient basis on which to establish obviousness. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

d. The skilled artisan would not be motivated to produce the presently claimed 3-component kit in order to allow the user to the drug:lipid ratio of the resulting pharmaceutical composition

The Examiner further suggests that the skilled artisan would be motivated to produce a kit having vinca alkaloids and liposomes in separate containers in order to be able to vary the amount of encapsulated vinca alkaloid. Applicants emphatically disagree with this

statement and submit that the skilled artisan would not wish to vary the amount of encapsulated vinca alkaloid when using a regulated drug for administration to a human patient.

As detailed in the accompanying Declaration of Dr. Thomas D. Madden, pharmaceutical products such as liposome-encapsulated vinca alkaloids are highly regulated by the United States Food and Drug Administration, pursuant to Section 21 of the Code of Federal Regulations. Pharmaceutical products intended for patient administration must meet strict specifications related to product formulation and dosages. In the case of liposomal drug products, these specifications include the drug concentration, lipid concentration, and drug:lipid ratio. The skilled artisan would appreciate that deliberately varying the amount of loaded drug could result in a product that fell outside the approved specifications, which would be both irresponsible and illegal. Therefore, the skilled artisan would much prefer to use pre-loaded liposomes, in order to ensure that the approved amount of drug was being administered to the patient and to minimize the possibility of error in preparing the final drug-loaded liposomes. Contrary to the Examiner's view, the possibility of producing liposomes containing varied amounts of drug would not motivate the skilled artisan to produce kits having drug and liposomes in separate containers.

For the reasons stated above, Applicants submit that the Examiner has failed to provide a line of reasoning establishing that the skilled artisan would be motivated to produce the claimed three-component kits, wherein drug and liposomes are provided separately. Accordingly, the Examiner has not established a *prima facie* case of obviousness over Webb. Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

2. Webb and Mehlhorn

Claims 71-79 and 81-85 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Webb in combination with Mehlhorn (5,762,957). The Examiner asserts that Webb discloses a method of preparing liposome-encapsulated vinca alkaloids that includes: (1) preparing vinca alkaloid solution; (2) preparing sphingomyelin/cholesterol liposomes with an acidic interior; and (3) adding disodium hydrogen phosphate to the external medium to create a pH gradient with an external pH of 7.2 to 7.6, which leads to the vinca alkaloid being loaded into

the liposome. The Examiner concedes that Webb fails to teach the supply of the reagents used in this method in the form of a kit. However, the Examiner asserts that Mehlhorn teaches kits for preparing drug-loaded liposomes and describes advantages of using such kits. These advantages include avoiding degradation of vesicles and leakage of drugs prior to administration. The Examiner further states that Mehlhorn is combined to show the knowledge in the art to supply material in the kit form where the drug is loaded using a gradient. The Examiner also states that it is within the basic skill in the art to supply the active agent separately from the disodium hydrogen phosphate solution taught by Webb, if the active agent is labile in this alkaline medium (Office Action mailed July 20, 2006, page 6, lines 1-2).

Applicants traverse this basis of rejection. The Examiner has failed to establish a *prima facie* case of obviousness, since, *inter alia*, he has failed to demonstrate that Webb, in combination with Mehlhorn, teaches each element of the presently claimed 3- component kits comprising: (i) a first vial comprising a vinca alkaloid solution; (ii) a second vial comprising liposomes comprising sphingomyelin and cholesterol and having an acid interior and exterior; and (iii) a third vial comprising a buffer solution having a pH higher than the pH of the solution in the second vial, such that combining the solutions of the second and third vials results in the pH of the exterior of said liposomes being neutral.. In addition, he has provided no evidence that the prior art taught or suggested modifying the teachings of Webb to produce the presently claimed kit.

a. <u>The combination of Webb and Mehlhorn fails to teach a kit comprising 3 components</u>

Webb and Mehlhorn, alone or in combination, fail to teach each element of the presently claimed kits. Specifically, they fail to teach a kit comprising three components, wherein the liposomes, the vinca alkaloid, and the buffer are provided as separate components. Clearly, Webb fails to describe a kit comprising three components. As described in detail in the Amendment submitted May 23, 2006, Mehlhorn teaches kits wherein the drug is present either in the vial containing the liposomes or the vial containing the buffer used to create a pH gradient.

Nowhere does Mehlhorn teach or suggest a kit wherein the drug is provided in a separate vial, as done in the presently claimed kits.

The Examiner argues that it would be within the knowledge of the skilled artisan to not include the drug in the basic buffer vial, if the drug was not considered stable at this pH. Even if this were true, Applicants submit that Mehlhorn's teachings that the drug is provided in either the acidic liposome solution or basic buffer solution would merely motivate the skilled artisan to provide the drug in the same vial as the liposomes. As noted in Dr. Madden's Declaration, this would be consistent with the knowledge at that time that vincristine exhibits optimal stability at pH 3.5 to 5.5 (Vendrig *et al.*). As the sphingomyelin:cholesterol liposomes are suspended in citrate buffer at pH 4.0 someone of ordinary skill would be motivated, if at all, to include the drug in the liposome vial. Prior to the filing of the instant application, therefore, there would have been no motivation to modify the teachings of Mehlhorn to provide the drug in a separate vial. Thus, the combination of Webb and Mehhorn fails to teach each element of the presently claimed kits.

b. The presently claimed 3-component kits possess surprising and unexpected advantages over the kits described by Mehlhorn

Applicants submit that the presently claimed kits possess unexpected advantages over the formulations and kits described by Webb and Mehlhorn. As discussed above, unbeknownst to Webb or Mehlhorn, vincristine is surprisingly unstable in the liposomes' interior. Since Mehlhorn teaches that the drug is present in the same solution as either the liposomes or the alkaline buffer solution, vincristine would also be unstable in the format of a kit taught by Mehlhorn. Vincristine was known to be unstable in alkaline solutions, and it would also have been unstable in the buffer containing the liposomes, since this aqueous environment is the same as in the liposomes' interior (see accompanying Declaration of Dr. Thomas D. Madden). Accordingly, the presently claimed kits provide an increased shelf-life over the kits described by Mehlhorn (comparable to the increased shelf-life obtained over the liposomal compositions described by Webb, *i.e.*, 2 years versus 6 months). This surprising attribute of the

presently claimed kits further demonstrates their nonobviousness over the teachings of the prior art, including Webb and Mehlhorn.

c. Webb and Mehlhorn fail to motivate the skilled artisan to produce the presently claimed 3-component kits

Applicants submit that the comments provided above, demonstrating that the presently claimed kits are not obvious over Webb alone, also apply to the instant basis of rejection. Accordingly, since Webb fails to provide any motivation to produce the claimed kits, a *prima facie* case of obviousness could only be established if Mehlhorn provided such motivation. This is not the case. The Examiner explicitly stated, "Mehlhorn is combined to show the knowledge in the art to supply material in the kit form where the drug is loaded using a gradient." Nowhere does the Examiner explain how Mehlhorn would motivate the skilled artisan to produce the presently claimed kit. Indeed, Applicants submit that Mehlhorn absolutely fails to provide such motivation.

Regarding the motivation allegedly provided by Mehlhorn to produce a kit for preparing drug-loaded liposomes, wherein the components are provided separately to avoid liposome degradation and drug leakage during storage, Applicants submit that this is not a valid motivation with respect to the presently claimed kits, which include liposomes comprising sphingomyelin and cholesterol. As described in Webb, such liposomes are associated with increased drug retention. Therefore, the skilled artisan would understand that the liposomal formulations described in Webb could be prepared and stably stored, and there would be no need to prepare such formulations immediately prior to use. Thus, the skilled artisan, having knowledge from Webb of the enhanced drug retention properties of sphingomyelin and cholesterol-based liposomes, would not be motivated by Mehlhorn's teaching regarding liposomes lacking this advantage, to produce the presently claimed kits.

Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection, in light of the above comments and further explanation.

3. ***Mehlhorn and Webb***

Claims 71-79 and 81-85 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Mehlhorn in view of Webb. The Examiner asserts that Mehlhorn teaches methods and kits for preparing liposome-encapsulated drugs, and that it would have been obvious to one of ordinary skill in the art, in light of Webb, to use vinca alkaloids as the drug of choice, since Webb teaches the same loading method as Mehlhorn.

Applicants traverse this basis of rejection and submit that the Examiner has not established a *prima facie* case of obviousness over Mehlhorn in light of Webb. The Examiner has failed to demonstrate that the cited references teach each element of the claimed invention and has also failed to demonstrate that Mehlhorn or Webb provide motivation to produce the presently claimed kits.

Applicants submit that the combination of Mehlhorn and Webb fails to teach each element of the claimed invention. As discussed in the previous Amendment filed May 23, 2006 and briefly above, the kits described by Mehlhorn are distinct from those presently claimed. Amongst other distinguishing features, the kits described by Mehlhorn contain the drug in either the same vial as the liposomes or the same vial as the buffer used to create the pH gradient. In the presently claimed kits, the drug is provided in a separate vial. Therefore, even in vinca alkaloid was substituted into a kit of Mehlhorn, the resulting kit would not include all features of the presently claimed kit.

Furthermore, Applicants again point out that the Examiner' statement that the loading method described in Mehlhorn is the same as that described by Webb is incorrect. Mehlhorn describes a pH gradient loading method wherein the pH of the solution exterior of the liposomes is basic. In contrast, the method described by Webb utilizes a gradient wherein the pH of the solution exterior of the liposomes is neutral. Accordingly, the pH of the resulting formulation prepared according to Mehlhorn must be adjusted to achieve a neutral pH prior to administration; whereas the formulation prepared according to Webb does not require further pH adjustment. In light of these differences in the methods, it naturally follows that kits for practicing the methods described by Mehlhorn would require different and/or additional components as compared to kits for practicing the methods described by Webb, even if the

skilled artisan was somehow motivated to prepare a kit for use according to method described by Webb. However, Applicants maintain the position that the skilled artisan would not be motivated to do so, for reasons discussed extensively above, including Webb's teaching that the sphingomyelin and cholesterol liposomes described therein have enhanced stability and increased drug retention properties as compared to other liposomes, including those described in Mehlhorn. Thus, Applicants respectfully submit that Mehlhorn, in view of Webb, fails to teach each element of the claimed invention and provides no motivation for the skilled artisan to alter or combine its teachings to achieve the presently claimed invention. Applicants respectfully request that the Examiner withdrawn this basis of rejection.

4. ***Webb and Mehlhorn and Lenk***

Claims 80 and 86 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Webb by itself or in combination with Mehlhorn or *vice versa*, further in view of Lenk. The Examiner asserts that that Webb and Mehlhorn teach kits comprising components for producing liposome-encapsulated vinca alkaloids, for the reasons described above. The Examiner concedes that these references do not teach the use of a cryoprotectact such as mannitol. However, the Examiner asserts that its inclusion in the kits taught by Webb, alone or in combination with Mehlhorn, would be obvious to one skilled in the art, since Lenk teaches that liposomes can be lyophilized using a cryoprotectant such as mannitol.

Applicants respectfully traverse this basis of rejection and submit that the Examiner has failed to make a *prima facie* case that the cited combination of references renders the kits of claims 80 and 86 obvious. Applicants submit that Lenk fails to remedy the deficiencies of Webb and Mehlhorn described above, and, therefore, the instant claims are not obvious in light of Webb, alone or in combination with Mehlhorn, further in combination with Lenk, for the same reasons detailed above with regard to claims 71-79 and 81-85.

As a final note, Applicants further submit that Webb, alone or in any combination with Mehlhorn, and further in view of Lenk, fails to teach each element of the kit of claim 86, including the specific concentrations and pHs of the solutions present in the recited kit. Thus, Webb, alone or in combination with Mehlhorn, in view of Lenk cannot render claim 86 obvious.

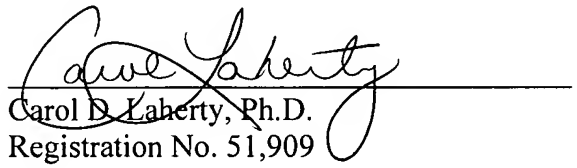
Applicants respectfully request that the Examiner reconsider and withdrawn this basis of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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Enclosure:
Declaration of Thomas D. Madden, Ph.D.

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